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Contribution of Noradrenaline, Serotonin, and the Basolateral Amygdala to Alcohol Addiction: Implications for Novel Pharmacotherapies for AUDs

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Abstract

Alcohol use disorders (AUDs) constitute one of the 10 leading causes of preventable deaths worldwide. To date, there are only a few Food and Drug Administration (FDA)-approved medications for AUDs, all of which are only moderately effective. The development of improved and effective strategies for the management of AUDs is greatly needed. This review focuses on understanding the neurobiological basis of alcohol addiction with a special emphasis on the role of serotonin (5-hydroxytryptamine, 5-HT) and noradrenaline (NE) in AUDs and sheds light on their complex interplay in the basolateral amygdala (BLA)—a brain region widely implicated in addiction. There is a significant evidence to support the role of the amygdala in stress-induced negative emotional states resulting from withdrawal from alcohol; in fact, it has been hypothesized that this leads to craving and relapse. Dysregulation of 5-HT and NE signaling in the BLA have been proposed to alter affective behavior, memory consolidation, and most importantly increase the propensity for addiction to alcohol and other common drugs of abuse. Improving deficits in 5-HT and NE receptor signaling may provide ideal targets for the treatment of AUDs.

Keywords: Addiction, alcohol use disorders, noradrenaline, serotonin, basolateral amygdala

1. Introduction

1.1 Alcohol addiction: one drink too many

Alcohol dependence or alcohol abuse, now collectively known as alcohol use disorders (AUDs), causes significant loss of productivity, health concerns, emotional instability, career-oriented failures, and socioeconomic problems [1]. It is estimated that AUDs amount to 3.8% of global deaths and 4.6% of disability-adjusted life years [2]. *The Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV-TR), defines AUDs on the persistence of dependence symptoms like tolerance, withdrawal, increased amounts of alcohol consumed over time, ineffective efforts to reduce use, interference with personal or professional life, significant amount of time spent obtaining, using, and recovering from alcohol or continued use of alcohol despite harmful consequences [3]. The U.S. National Institute of Alcohol Abuse and Alcoholism (NIAAA) defined men who consume more than 14 drinks per week and women having more than 11 drinks per week belong to the "At Risk" category of alcohol consumers.

1.2 Neurobiology of alcohol addiction: a vicious cycle

Alcohol addiction like any other drug addiction is a chronic relapsing disorder characterized by compulsive alcohol use and alcohol-seeking behavior [4, 5]. The neurobiology of alcohol addiction is increasingly complex; however, for the purpose of simplicity, it can be delineated in three stages. The first phase of this cycle is the *Binge and intoxication stage* [5]. During this phase, reward areas of the brain involving the mesocorticolimbic system like the dorsal striatum and nucleus accumbens (NAc) are activated, which results in pleasurable and rewarding feelings [5, 6]. Dopamine is a key neurotransmitter involved in this stage [7–9]. The positive reinforcement is triggered by the pleasurable effects of alcohol where the user wants "more" to experience the hedonic effects. This is then followed by the *Withdrawal stage* [5]. During this phase, brain regions that are associated with negative feelings and emotions are activated, such as the amygdala and bed nucleus of stria terminalis (BNST) [4, 5]. Chronic withdrawal-induced stress blunts the activity of the stress–response system and sensitizes extrahypothalamic structures of the extended amygdala [6, 10]. This stage marks a critical phase in the addiction cycle where alcohol use is primarily motivated by the desire to avoid negative feelings of stress, dysphoria, and negative emotional states of alcohol withdrawal. The third phase is the *Preoccupation and anticipation stage* [5]. During this phase, brain regions like the frontal cortex and hippocampus [11] that respond to previously paired alcohol cues and contexts are activated, intensifying alcohol-seeking behavior [12, 13]. Since the frontal cortex is involved in decision-making and higher executive functions, alcohol-induced neuroadaptations of the frontal cortex [14] impair higher cognitive and decision-making processes, increasing the rate of relapse in alcoholics.

Over time, as this cycle is repeated, alcohol-induced neuroadaptations in the reward circuitry, stress–response pathway, and brain regions involved in higher cognitive functions facilitate the transition from nondependent to dependent alcohol consumption. These maladaptive neuromodulations contribute to sensitization, tolerance, craving, and relapse to alcohol-seeking [4]. For instance, alcohol-induced plasticity in glutamatergic signaling in the NAc may

contribute to behavioral sensitization to the effects of alcohol [15], while changes in the synaptic properties of NAc-medium spiny neurons contribute to relapse during withdrawal [16]. Furthermore, chronic alcohol modulates presynaptic and postsynaptic functions on glutamate neurons in the basolateral amygdala (BLA) [17]. Finally, alcohol impairs communication between the amygdala and prefrontal cortex to disrupt cognitive and emotional responses that lead to altered affective states that further contribute to the development of alcohol dependence [18, 19].

1.3. Pharmacotherapy: available treatment options for AUDs

Bill Wilson and Bob Smith took early steps toward alcohol remediation in 1935 with the introduction of Alcoholic Anonymous (AA) [20, 21]. This 12-step approach toward rehabilitation was built on the premise of acceptance of individual helplessness during addiction to alcohol and other drugs of abuse [22]. This method was adopted by the "Minnesota model of addiction treatment" in a 28-day rehabilitation setting [23]. Parallel efforts to treat alcoholism by understanding the nature and cause of alcohol dependence were gaining momentum, which led to the foundation of the National Institute of Alcohol Abuse and Alcoholism (NIAAA) in 1970 [24].

Since then, several approaches to understand and treat alcoholism were designed that took into consideration individual differences and susceptibility to AUDs. Cognitive behavioral therapy or motivational therapy was adopted as the first line of treatment to match the needs of the addict to help recuperate in a 12-week therapy session called "Project MATCH" [25]. This project was successful in rehabilitation of patients that did not have any psychiatric conditions. The next step was to combine behavioral and pharmacotherapy in the treatment of alcoholism called "Project COMBINE" [26]. This study evaluated the efficacy of available pharmacotherapies, namely acamprosate and naltrexone, in conjunction with or without medical assistance and with or without cognitive–behavioral therapy [27].

Acamprosate (Campral™), the calcium salt of N-acetyl homotaurine, suppresses alcohol consumption and relapse [28, 29]. Early reports delineating the mechanism of action of acamprosate were unclear [30]; however, recent studies have shown that acamprosate works through the calcium ion in its molecular structure [31]. This was supported with improved results in patients that showed an increase in plasma calcium levels following acamprosate treatment [31]. Acamprosate has been shown to have a good safety and a tolerability profile and is highly effective in maintenance of abstinence in patients who are abstinent at treatment initiation [32].

In addition to acamprosate, the mu-opioid receptor antagonist, naltrexone (Re Via™), was found effective as a treatment for alcohol consumption and relapse [33]. However, studies have shown that naltrexone is ineffective in achieving abstinence in alcoholic subjects; instead it is more effective to reduce consumption [34, 35]. Also, recent research demonstrated that it acts more specifically for a cohort with single nucleotide polymorphism (SNP) in exon 1 of the mu-opioid receptor gene (*OPRM1*) [36] limiting broader efficacy. Nevertheless, naltrexone reduces alcohol consumption through a dopaminergic/opioidergic reinforcement system, causing increased sedation and less arousal in patients consuming alcohol [35]. Both these drugs were

successful in reducing drinking in combination with behavioral therapy, as highlighted by the COMBINE project [37].

In addition to acamprosate and naltrexone, disulfiram (Antabuse®) was approved as a therapeutic treatment for alcoholism. The anti-alcohol addiction properties of disulfiram were serendipitously discovered, when a Danish physician Jacobsen accidentally ingested alcohol over disulfiram and experienced its unpleasant and nauseous effects [38, 39]. Disulfiram inhibits the enzyme aldehyde dehydrogenase (ALDH), which results in the accumulation of acetaldehyde on alcohol ingestion [40]. This toxic metabolite produces aversive symptoms, such as flushing, nausea, and vomiting, and a desire to avoid this reaction encourages abstinence [41]. Disulfiram also inhibits dopamine-β-hydroxylase (DBH), the enzyme required to synthesize noradrenaline (NE). It reduces NE concentrations and elevates dopamine (DA) concentrations to facilitate normal DA functioning [40, 41], a pharmacotherapeutic feature of the drug that makes it an excellent treatment option even for cocaine addicts.

In addition to this, our lab has investigated the role of neuronal nicotinic acetylcholine receptors in alcohol addiction and came up with varenicline (Champix™) as a treatment option for AUDs [42, 43]. Varenicline was found to be more efficacious in heavy-drinking smokers because of the comorbid nature of both the types of addiction involving the recruitment of nicotinic acetylcholine receptors. Varenicline is now in its third stage of clinical trial as a treatment option for AUDs [44, 45].

1.4. Shortcomings of available treatment options for AUDs: need for better pharmaceutical alternatives

Acamprosate, naltrexone, and disulfiram are the only available medications for alcoholism approved by the Food and Drug Administration (FDA), while nalmefene (Selincro™), an opioid receptor antagonist having a similar mechanism of action to naltrexone [46], is approved as a medication for alcohol abstinence in Europe [47]. Most of these drugs treat one aspect of alcoholism at best without significantly altering other parameters of alcohol addiction.

Drugs like acamprosate reduce consumption and are effective in motivating abstinence for a certain period of time. However, acamprosate does not significantly affect abstinence-induced rebound consumption of alcohol [48]. Also, despite achieving an aversion for alcohol, the likelihood of the addict returning to drinking with increased tolerance cannot be assured. A case study also indicated the development of Parkinson's-like syndrome with acamprosate use [49].

Although naltrexone was shown to be very effective with and without cognitive behavioral therapy, noncompliance with maintenance of drug regimen was shown to limit efficacy [50]. About 37% patients were reported to discontinue naltrexone therapy by 12 weeks and 80% by 6 months [50]. It is possible that some of the severe complications involved with naltrex-one use, that is, renal failure and hepatitis, may have contributed to its early discontinuation [51]. Furthermore, the efficacy of naltrexone appears to be related to alcohol abusers having the mu-opioid SNP [36].

All the above drugs work best when combined with an individual's motivation to quit drinking. Disulfiram works on this principle as it deters the positive reinforcing effects of alcohol and masks them with aversive and negative feelings stimulated by the action of the drug post-alcohol consumption [52]. As a result, this drug is effective for alcoholics with a goal to achieve complete abstinence, but has limited efficacy for alcoholics without these goals. Noncompliance is one of the biggest challenges in the use of disulfiram, illustrated by the 20% compliance measure in the largest controlled trial to date [53]. Also, disulfiram is contraindicated in patients with cardiac disease and on rare occasions may cause severe liver damage [54].

Despite the availability of these pharmacotherapies and behavioral therapy, AUDs are widely prevalent. As illustrated by COMBINE, no single medication or treatment strategy is effective in every case or in every person [37]. A detailed investigation of other neurobiological factors that play a role in alcohol dependence is needed as are further strategies to treat alcoholism.

The remainder of this chapter highlights the role of serotonin (5-hydroxytryptamine, 5-HT), NE, and BLA in alcohol addiction with a view to improve current treatment strategies for AUDs.

2. NE and serotonin: role in alcohol dependence

Prolonged alcohol exposure causes maladaptive changes in regions of the extended amygdala that cause sensitization to negative emotional states and reinforcement of addictive behaviors during withdrawal. These neuroadaptations alter the activity of important neurotransmitters particularly involved in stress. Such changes are well documented for increasing the activity of the stress neurotransmitter corticotrophin-releasing factor (CRF) in rodent models of alcohol dependence [4]. Additionally, changes in the function and signaling of other neurotransmitters including 5-HT [55–57] and NE [55–61] have also been implicated in the development of alcohol addiction.

NE and 5-HT play a crucial role in regulating mood, emotions, and importantly, behavioral adaptations to stress that include addictive phenotypes [57, 60]. As these neurochemicals widely innervate the reward system [62–66] and extrahypothalamic regions involving the amygdala [67–71], these are prime candidates to influence alcohol and even other drug-seeking behaviors.

Dysregulation of the 5-HT pathway is implicated in AUDs and other affective states like depression and anxiety disorders [57, 72, 73]. Recent studies have demonstrated an increase in the immunoreactivity of tryptophan hydroxylase (TRH)—the rate-limiting step in 5-HT synthesis, in the dorsal raphe nuclei (DRN) of alcohol-dependent victims of depression and suicide compared to normal psychiatric controls [74]. Such disruptions in brain serotonin levels in these individuals have widespread implications in the role of 5-HT to regulate emotional and behavioral vulnerability to alcohol and other drugs of abuse. Alcohol increases 5-HT levels in the ventral tegmental area (VTA), NAc, and amygdala [75]. These brain regions play a

pivotal role in processing of information from emotional and rewarding stimuli. Chronic alcohol abuse alters the activity of these brain areas, resulting in changes in motivational and goal-directed behaviors, which further drive alcohol-seeking behavior [76, 77]. For instance, studies have shown that behavioral sensitization to alcohol is mediated by accumbal 5-HT_{2C} receptors [76], and blockade of 5-HT_3 receptors especially in the VTA attenuates alcohol consumption [77]. The 5-HT receptors, 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, and 5-HT_{2C}, [78–80] have been widely implicated in alcohol consumption in animal models with new evidence also implicating 5-HT_3 and 5-HT_6 receptors in alcohol addiction [81, 82].

NE has been shown to play a significant role in negative emotional states which contribute to alcohol consumption [60, 83, 84]. Acute alcohol decreases [85], while chronic alcohol and withdrawal increases the activity of neurons in the locus coeruleus (LC), a region that provides the majority of NE in the brain [86]. Activation of the α2-adrenergic autoreceptors has been shown to attenuate the overall negative effects of withdrawal [87], and blocking α1-adrenergic receptors (ARs) using prazosin reduced alcohol consumption in dependent rats [88] and human alcoholics [89]. Likewise, treatment with the β-AR antagonist, propranolol, reduced drinking in dependent rats [60]. Evidence also suggests that β-ARs may also contribute in mediating the anxiolytic effects of alcohol [58].

Furthermore, CRF is a regulating factor in the activation of the hypothalamus–pituitary–adrenal (HPA) axis to stress [90–94]. Chronic alcohol consumption affects CRF signaling in the central nucleus of amygdala (CeA) and BNST, as evidenced by alterations in CRF transmission during withdrawal [95]. Interestingly, NE and 5-HT have been shown to interact with the neurotransmitter CRF in neuroanatomical sites like the LC, DRN, CeA, and BNST [96–100] to influence addictive behaviors. For instance, yohimbine, a pharmacological agent used to promote stress in rats, has effects on NE, 5-HT, and CRF signaling to potentiate alcohol drinking and reinstatement [101, 102], suggesting possible mutual regulatory roles of these neurotransmitters in alcohol dependence and relapse. This was further evidenced by CRF antagonism in the DRN to attenuate yohimbine-induced alcohol-seeking behavior in rats [100]. Also, CRF and NE antagonism has been shown to be effective in reducing stress-induced reinstatement in human alcoholics [88, 103].

3. The BLA: role in alcohol addiction

The amygdaloid complex is made up 13 distinct nuclei which are divided in three groups: the deep or basolateral group, the superficial or cortical-like group, and the centromedial group [104]. These nuclei have been proposed to be located in such a way to maximize the amygdala's connections with other limbic, cortical, and subcortical regions of the brain to help facilitate its function in emotional processing, learning, and fear memory [105–107]. The basolateral amygdalar complex, comprising of lateral amygdala (LA), basal and basomedial nuclei [108, 109] controls behavioral expressions like emotional arousal, fear, and stress that are linked to traumatic incidents, stressful environmental stimuli, or pharmacological stressors, and consolidates them as memories [70]. The BLA communicates through excitatory efferents to

the prefrontal cortex and structures of the limbic system involving the hippocampus, NAc, dorsomedial striatum (DMS), and BNST [110–114], while it receives feedback from these structures through glutamatergic afferents [115, 116], majority of which converge with the cortical inputs [114] running toward the BLA.

The role of the BLA in fear, memory consolidation, and emotional learning along with its contribution in associative learning for appetitive conditioning is well documented [70, 105, 117, 118]. Since the BLA can impart incentive salience to a previously neutral stimulus in response to a motivational or a goal-directed task [119], recent efforts have now focused on the role of the BLA in drug-seeking, including cocaine [120], morphine [121], and alcohol [122–124].

Alcohol has been shown to increase neuronal activity and glucose utilization in the BLA [125]. Additionally, long-term alcohol exposure alters glutamate transmission in the BLA [126] and NAc [127], which is implicated in increased alcohol self-administration in rodents [128]. Furthermore, alcohol-induced withdrawal stress increases presynaptic glutamatergic function in thalamic afferents to the BLA that may explain the increased emotional dysregulation during withdrawal [129]. It has also been shown that altered neuropeptide S function in the BLA following long-term alcohol exposure may contribute to relapse [130]. Furthermore, a recent study has shown that IL-1 receptor signaling in the BLA contributes to binge-like alcohol consumption in mice [131].

There is growing body of evidence that supports the role of the BLA in conditioned–cued relapse [132] and context-induced reinstatement [133] for alcohol and a variety of other drugs [134–137]. It was shown that the BLA may play a significant role in cue-induced alcohol reinstatement [138], following exposure to previously alcohol-paired environmental cues [123]. Research has also shown that BLA–glutamatergic signaling attributes salience to conditioned cues that are related to alcohol-seeking [132], while the opioidergic system of the BLA may play a role in context-induced alcohol-seeking [140]. Indeed, since the BLA extensively communicates with the NAc, alcohol withdrawal-induced changes in glutamatergic function in the BLA get perpetuated in structures of the reward system that may contribute to craving and relapse [141].

It is well documented that repeated and chronic stress leads to adverse behavioral outcomes, and many studies support the reinforcing effects of chronic stress in drug addiction in animal models [86, 142–144]. Stress alters the morphology of BLA principal cells and impairs fear extinction memory [145] that may have implications in the development of affective disorders like PTSD and depression. It has been shown that the BLA modulates chronic stress-induced learning and memory deficits in the hippocampus, suggesting that dysregulation of BLA–hippocampal signaling may affect memory storage, retrieval, and extinction of fear memory that may contribute to emotional disorders and drug dependence [146]. Furthermore, early life stress causes increased excitability of pyramidal cells in the BLA [147], while chronic restraint stress in adolescent and adult rats increases BLA activity [148]. Increased BLA excitability has been positively correlated with increased anxiety and increased alcohol-seeking behavior [141, 147, 149, 150].

Long-term exposure to alcohol simulates chronic stress-like conditions [130] that have a profound effect on fear memory consolidation [151]. Alcohol withdrawal-induced stress has been shown to increase conditioned fear [152] and impair extinction of fear memory [153]. A recent study also showed that repeated alcohol exposures enhance retrieval of previously consolidated fear memories and augments activity in BLA and other brain regions involved in fear memory retrieval [154].

4. Role of 5-HT and NE in the BLA in alcohol addiction

There is significant evidence that supports the role of NE and 5-HT in drug dependence and alcohol addiction [87, 155–157]. Moreover, the BLA which is highly implicated in dependence to alcohol-seeking [17, 123, 131, 132] is densely innervated by these neurotransmitters [58, 71, 158, 159]. Since chronic alcohol exposure causes neuroadaptations that affect the signaling and receptor subtypes of these neurotransmitters, dysregulation of NE and 5-HT transmission in the BLA may lead to a constellation of aversive outcomes including altered consolidation of alcohol-related memories, anxiety disorders, and eventually higher rates of relapse [132, 138].

NE plays a vital role in facilitating the function of the BLA in fear memory consolidation [70]. It has been shown that intra-BLA infusions of β-AR agonists enhance retention of inhibitory avoidance [160], while β-AR antagonists block fear memory enhancement [69]. Also, α_1-AR activation in the BLA enhances fear memory consolidation through an interaction with β-ARs [161]. This evidence suggests that noradrenergic receptors strongly contribute to BLA function. It is possible that alteration in NE activity in the BLA may lead to altered memory consolidation and stress-coping mechanism that may enhance alcohol-seeking and relapse [162]. Indeed, antagonism of α_1-ARs reduced dependence-induced increase in alcohol consumption in rats [88]. Furthermore, recent evidence supports the role of β-ARs in alcohol-induced enhancement of GABA synapses in the BLA, suggesting a possible noradrenergic mechanism mediating the anxiolytic effects of alcohol [58] (**Figure 1**). This was further evidenced by intra-BLA infusions of a β_3-AR agonist that enhanced inhibitory GABA signaling on BLA pyramidal cells to reduce anxiety-like and alcohol-seeking behavior [163]. Furthermore, the neuroadaptive changes associated with chronic alcohol consumption including desensitization of β-ARs in the BLA have been shown to modulate its activity [164] (**Figure 1**).

In contrast to excitatory dopaminergic/glutamatergic signaling in the BLA that increases its activity, serotonergic transmission in the BLA is inhibitory [165]. The serotonergic innervations on principal glutamate cells in the BLA decrease the overall excitatory activity of these cells [166] through 5-HT$_{1A}$ receptors [167] and modulate BLA output (**Figure 2**). This is supported by a recent study where depletion of serotonin in the BLA increased glutamate receptor density and fear-potentiated startle in mice, indicating that serotonergic inhibition regulates excitatory signaling in the BLA to modulate affective behaviors like anxiety [68].

Chronic alcohol-induced neuroadaptations change 5-HT receptor expression and function in the brain [168] that alters the regulatory control of serotonin over BLA principal cells. Loss of inhibition on BLA principal neurons increases BLA output, increasing anxiety [169, 170] and other symptoms of withdrawal. In support of this, chronic alcohol or withdrawal stress increases the expression of $5\text{-}HT_{1A}$ autoreceptors in the raphe nucleus [168] which causes a reduction in 5-HT levels in the BLA. This increases BLA activity, which contributes to anxiety-like behaviors following withdrawal from chronic alcohol (**Figure 2**). Furthermore, $5\text{-}HT_{2A/2C}$ receptors have been suggested to potentiate inhibitory GABAergic tone on principal BLA glutamatergic cells to decrease excitability [67]. Chronic alcohol causes adaptive changes that lower the expression levels of these receptors, reducing inhibition over BLA principal neurons [67]. This augments BLA output and increases the possibility of anxiety-induced relapse following a period of chronic alcohol exposure [141] (**Figure 2**). In addition to this,
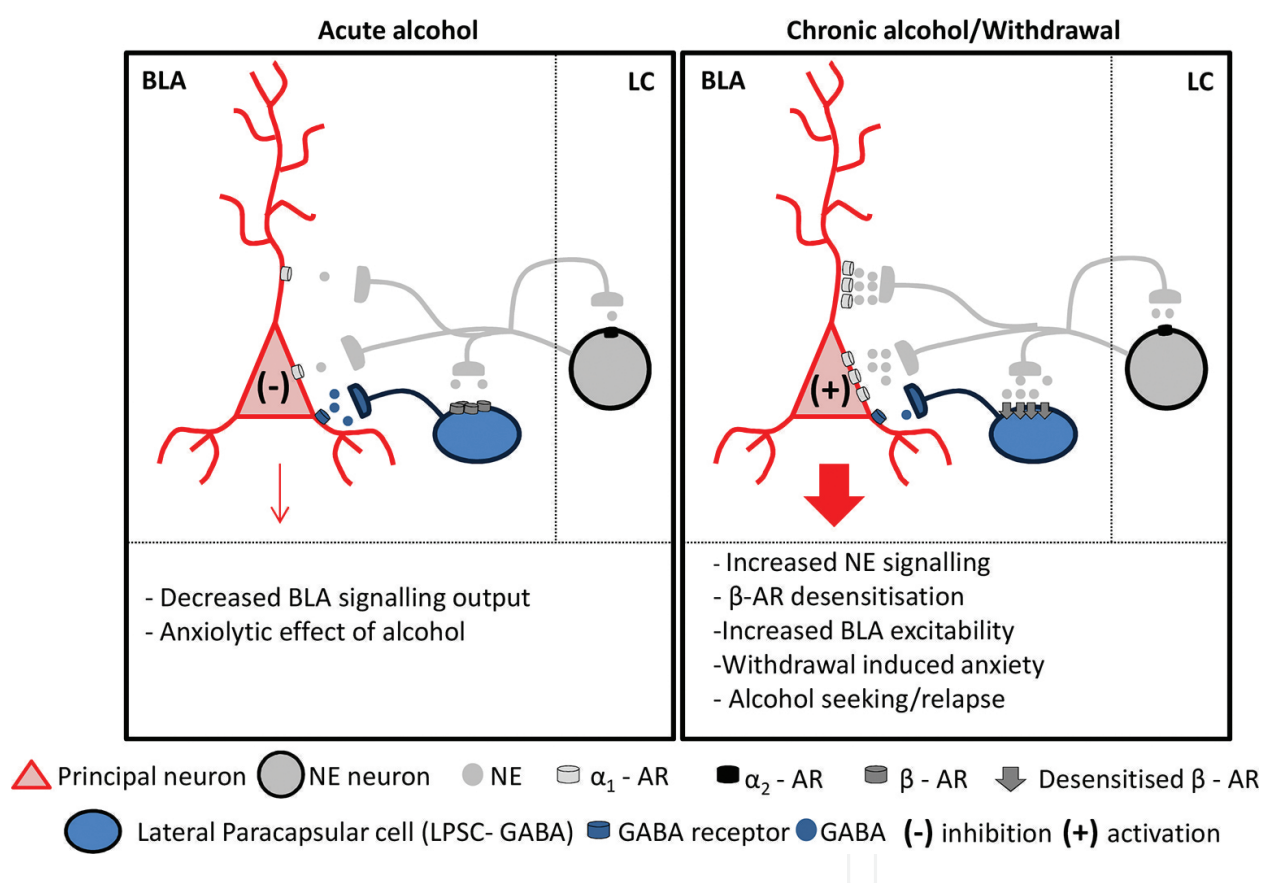
Figure 1. Changes in NE signaling and BLA output following acute and chronic alcohol exposure or withdrawal. Acute alcohol decreases NE signaling in the BLA, which is regulated by a feedback loop through presynaptic α_2-adrenergic autoreceptors expressed on NE fibers in the LC. Decreased BLA-NE levels decrease the excitation of BLA principal cells through postsynaptic α_1-ARs. Acute alcohol further enhances the inhibition of BLA principal cells by NE-mediated enhancement of GABA synapses through β-ARs expressed on GABAergic LPSCs. The net result of this inhibition is decreased BLA principal neuron excitability and BLA activity which has been suggested to reduce anxiety and may explain the anxiolytic effect of acute alcohol. Chronic alcohol/withdrawal increases NE levels that enhance α_1-AR mediated excitation of BLA principal cells. Chronic ethanol has been shown to desensitize β-ARs in the brain which leads to a reduction in NE's effects on GABA-LPSCs causing a decrease in the inhibitory tone over BLA principal cells, increasing excitability. This increases the net excitability of BLA principal cells and increases BLA activity causing anxiety during withdrawal and may contribute to alcohol-seeking and relapse.

chronic alcohol-induced neuroadaptations in other receptor subtypes like the GABA-A receptors facilitate the anxiolytic effects of alcohol [171]. Increasing the activity of 5-HT on GABA-A receptors on BLA principal cells may contribute in reducing withdrawal-induced anxiety and alcohol-seeking.
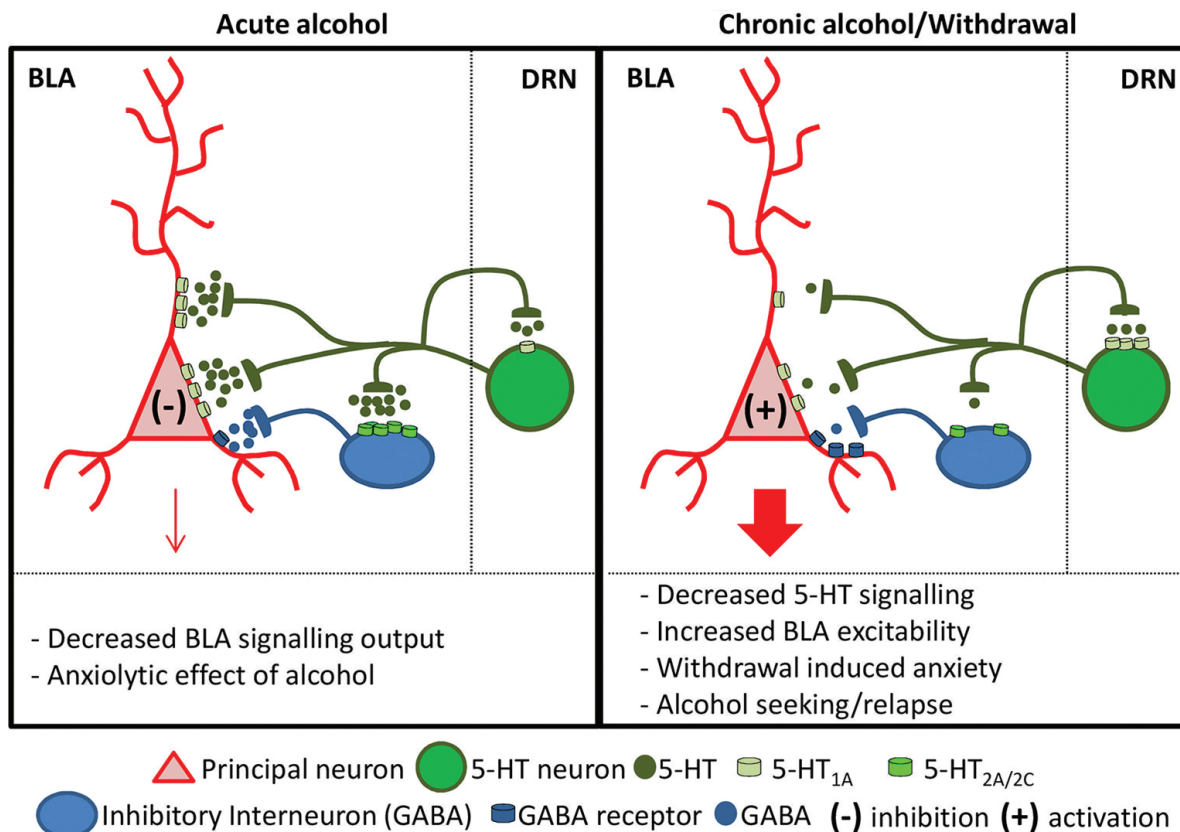
Figure 2. Changes in 5-HT signaling and BLA output following acute and chronic alcohol exposure or withdrawal. Acute alcohol increases 5-HT release in the BLA which is regulated by a feedback loop through 5-HT$_{1A}$ autoreceptors expressed on 5-HT neurons in the DRN. Increased BLA-5-HT levels enhance the inhibition of BLA activity through postsynaptic 5-HT$_{1A}$ receptors expressed on principal neurons. Increased 5-HT signaling also activates 5-HT$_{2A/2C}$ receptors expressed on GABAergic interneurons in the BLA that further increase the inhibition on BLA principal cells through increased GABAergic tone. The net result of this inhibition is decreased BLA principal neuron excitability and BLA activity, which has been shown to reduce anxiety and may explain the anxiolytic effect of acute alcohol. Chronic alcohol/withdrawal increases the expression of 5-HT$_{1A}$ autoreceptors in the DRN which decreases 5-HT levels in the BLA. This reduces 5-HT$_{1A}$-mediated inhibition on BLA principal cells. Chronic alcohol-induced withdrawal downregulates the expression of 5-HT$_{2A/2C}$ receptors on GABAergic interneurons to further decrease the inhibitory GABA tone on BLA principal cells, increasing excitability. Chronic alcohol also upregulates GABA receptors on principal cells. This results in a net increase in BLA activity causing anxiety that may contribute to alcohol-seeking and relapse.

Furthermore, cross-modulation of synaptic transmission in the BLA by 5-HT$_{1A/1B}$ receptors and β-ARs dictates BLA output [159] that may affect behavioral outcomes like stress, anxiety, and drug dependence. In support of this, we have shown that pindolol, a drug having dual pharmacological activity on 5-HT$_{1A/1B}$ receptors and β_1/β_2 ARs, decreases alcohol consumption in mice following long-term alcohol exposure. Our electrophysiological experiments also indicate that the BLA may mediate the effects of pindolol on alcohol consumption [172].

5. Conclusion

Research in the past few decades has significantly increased our understanding of the neurobiological basis of alcohol dependence. Recent research has targeted pathways that mediate more than just the reinforcing properties of alcohol. However, despite these concerted efforts, effective pharmacological interventions for the management of AUDs remain elusive.

Chronic alcohol consumption causes maladaptive changes in brain regions like the extended amygdala that cause sensitization to negative emotional states of withdrawal. These changes disrupt the signaling of many neurotransmitters including those involved in stress. Dysregulation of NE and 5-HT signaling has been widely implicated in the development of affective disorders and alcohol addiction. Specifically, NE and/or 5-HT impairments in the BLA, a region involved in stress, emotional processing, and reward-seeking have been suggested to play a major role in the development of alcohol dependence (**Figures 1** and **2**).

In addition to the growing evidence in animal models of alcohol addiction, pharmacological compounds that target NE and 5-HT receptors have also shown promise as potential treatment strategies for AUDs in human patients [173, 174]. Noradrenergic compounds like propranolol [175, 176] and atenolol [174] have been shown to attenuate alcohol-seeking behavior and reduce craving in human alcoholics. Similarly, serotonergic compounds like buspirone show efficacy to reduce anxiety-induced consumption in alcoholics [177, 178]. Moreover, our research indicates that pindolol, the FDA-approved antihypertensive drug having activity on both 5-HT and NE receptors, may have a similar mechanism of action to more effectively reduce alcohol consumption following chronic intake [172].

Since the BLA plays a vital role in affective disorders and stress-induced maladaptive behavioral conditioning, drugs that selectively modulate NE and 5-HT signaling in the BLA offer great promise in the treatment of AUDs. With the increasing need for improved pharmacotherapeutic strategies for the management of AUDs combined with the modest efficacy of current treatments, putative compounds that target 5-HT and NE receptors may prove useful for the development of more effective treatment strategies for alcohol dependence.

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Author's contributions

All authors have been involved in the preparation and have approved the submitted manuscript. Omkar Patkar was the lead author and responsible for conducting the literature review and writing the manuscript. Arnauld Belmer assisted in writing and editing the manuscript. As the senior author, Selena Bartlett supervised Omkar Patkar's work, reviewed, and edited the manuscript.

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